Estrogen Replacement Therapy and Risk of Ovarian Cancer in Postmenopausal Women

To the Editor: Dr Lacey and colleagues[1] reported an increased risk of ovarian cancer in women who used unopposed estrogen, but not among women who used an estrogen-progestin combination. However, the histology of these tumors was described for only one third of the cases. A significant difference was found only for endometrioid cancers. Another study had similar findings, with only a significant increase in endometrioid and clear cell epithelial cancers among women receiving unopposed estrogen.[2] In that study, the risk was greater in women who had received a tubal ligation or a hysterectomy, thus suggesting a possible role of estrogen-stimulating endometriosis.

However, the data concerning the risk of estrogen and ovarian cancer are not consistent. A recent meta-analysis did not find an association between estrogen replacement therapy (ERT) and ovarian cancer.[3] The literature suggests that the risk, if any, may be confined to specific histologic subgroups of ovarian cancer.

There are several reasons to assume that estrogen may selectively increase the risk of epithelial cancer. It has been observed that tumors with a high expression of estrogen receptors and an increase in proliferation in areas of high estrogen-receptor density have less apoptotic activity.[4] An inhibition of apoptosis by estradiol may be due to an increase of Bcl-2 messenger RNA and protein levels.[5] The surface epithelium of these tumors secretes estradiol and aromatase is functionally expressed, playing an active role in altering its own hormonal environment and promoting tumor progression. Estrogen also induces other factors that may increase cancer risk.[6]

Conversely, high levels of progesterone appear to exert marked inhibitory effects on ovarian epithelium. Progestins induce differential regulation of transforming growth factor β, a change in expression that is highly associated with apoptosis.[7]

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To the Editor: Dr Lacey and colleagues[1] found a significantly increased risk of ovarian cancer in women who used unopposed ERT, but not ERT with progestins. We are concerned that the sample was atypical in that most had a history of suspicious breast lumps. Eighty-four percent of the person-years on which the relative risk estimates were calculated were derived from women who were recommended to have surgery or had surgery for breast lumps.

In fact, women with benign lumps are at an increased risk of breast cancer with relative risks as great as 16—depending on the nature of the lesion.[2] Women with breast cancer have a higher risk of subsequent ovarian cancers.[3] Associations between unopposed ERT and ovarian cancer in women at higher risk of breast cancer may not necessarily apply to the general population. Even if an association exists, as suggested by some studies referenced by the authors, this must be placed in perspective. The lifetime risk of ovarian cancer in the general population is about 1.4%, but in women who have had a hysterectomy—the group most likely to be prescribed unopposed ERT—this risk is reduced by a third.[4] An increase of 7% per year of use of a 1% lifetime risk should be seen in the context of the benefits of ERT.

Approximately half of all healthy postmenopausal women have low bone mineral density and increased risk of fractures[5]; estrogen use reduces this risk.[6] The only clinically effective therapy for menopausal vasomotor symptoms is ERT. It is associated with a 36% reduction in colorectal cancer,[6] the third most common cancer in women, with a lifetime risk of 6%. Therefore, we believe that the ovarian cancer risk should not unduly alarm women with a prior hysterectomy who are weighing the pros and cons of ERT use. However, women in

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Letters Section Editor: Stephen J. Lurie, MD, PhD, Senior Editor.

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their late 40s, who are recommended to have a hysterectomy, may need to consider the findings of Lacey and colleagues.

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In Reply: We interpret our and others' data differently than do Drs Burry and Cain. It is true that women with short-term estrogen-progestin replacement therapy did not have increased risk of ovarian cancer in our study, but there are insufficient data to adequately assess risk associated with short-term and longer-term postmenopausal estrogen plus progestin use. Our article addressed both studies that Burry and Cain mention and we explained why that meta-analysis[1] provides more support for an increased risk than a null association.

Neither our data nor another recent study[2] provide evidence that only certain histologic types are associated with ERT. Ovarian cancers identified via death certificates generated most of our missing histologic data. We and others[3] reported increased risks in analyses restricted to fatal ovarian cancer, in which nonendometrioid types may be overrepresented.[4] Histologic misclassification of ovarian cancer limits the current utility of histology-specific associations.[5]

The comments of Dr Gilbert and colleagues alerted us to a typographic error in our article. We mistakenly switched the "BCDDP Participant Type" row headings for the last 2 rows on page 336. Using the correctly labeled data, participants who had had breast surgery but no malignant disease, or were recommended for surgery, contributed 58% of the total person-years in the analysis. Adjustment for participant type did not change our results. Increasing duration of ERT-only use was associated with ovarian cancer in participants with prior breast surgery or recommended for surgery, as well as in participants who had neither had surgery nor recommendation for surgery (TABLE).

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Table. Duration of ERT-Only Use Type*

	Duration of ERT-Only Use, y†					*P* Value for Trend	Increase in RR (95% CI) per Year of Use
	None	<4	4-9	10-19	≥20		
Breast Surgery or Recommended for Surgery in BCDDP							
Person-years	156 418	54 999	23 614	17 400	6984		
No. of ovarian cancers	69	38	14	10	8		
Mean person-year weighted duration of ERT-only use	0	1.4	6.3	13.8	25.2		
Mutivariate-adjusted RR (95% CI)‡	1.0 (Referent)	1.8 (1.2-2.7)	1.7 (0.93-3.0)	1.8 (0.87-3.5)	3.8 (1.7-8.5)	.01	0.06 (0.01-0.15)
No Surgery Performed or Recommended in BCDDP							
Person-years	114 102	38 805	16 837	12 658	4583		
No. of ovarian cancers	51	13	11	11	8		
Mean person-year weighted duration of ERT-only use	0	1.4	6.3	13.9	25.9		
Mutivariate-adjusted RR (95% CI)‡	1.0 (Referent)	0.76 (0.41-1.4)	1.5 (0.77-3.0)	1.8 (0.86-3.6)	2.5 (1.1-5.9)	.004	0.08 (0.02-0.18)

*ERT indicates estrogen replacement therapy; BCDDP, Breast Cancer Detection Demonstration Project; RR, rate ratio; and CI, confidence interval.
†Duration of use was unknown for 3185 person-years and for 3 women who developed ovarian cancer.
‡Adjusted for attained age, menopausal type (natural, surgical, or unknown), and duration of oral contraceptive use (none, ≤2 years, or >2 years).

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Differences in Success Rates of Noninvasive Ventilation

To the Editor: Dr Keenan and colleagues[1] found that noninvasive ventilation (NIV) did not improve outcomes in patients who developed postextubation acute respiratory failure (ARF). This result was unexpected and conflicts with recent literature.

In a prospective observational study, for instance, NIV was found to avoid reintubation in 18 of 21 consecutive patients who developed ARF after bilateral lung transplantation, mainly for cystic fibrosis.[2] Among those who responded to NIV, oxygenation and respiratory acidosis were improved, with a low rate of complications and no mortality in the intensive care unit (ICU). The first prospective randomized controlled study, in the ICU setting,[3] demonstrated that NIV was safe and effective in reducing the need for reintubation and improving in-hospital and 3-month survival in 24 patients with hypoxemic ARF after lung resection compared with standard medical treatment. Furthermore, when correctly set, noninvasive ventilation can improve gas exchange, breathing pattern and decreases the work of breathing in patients with nonchronic respiratory failure (CRF) with persistent ARF after early extubation,[4] as well as those with CRF who are not ready to sustain totally spontaneous breathing.[5] These findings suggest that NIV may replace conventional mechanical ventilation in some circumstances.

The study by Keenan et al is in fact the first prospective randomized controlled study that failed to find a benefit for NIV in the postextubation setting. The authors report that their unexpected results may have been related to their population heterogeneity, severity of the respiratory distress included as well as the lack of double-blinding for cointerventions, and the limited NIV experience of the staff.[1] However, it would have also been of interest to provide the causes for postextubation ARF. This could help explain the high rate of reintubation and the short time from extubation to ARF reported in both groups. Similarly, extubation criteria were defined but no weaning protocol from mechanical ventilation was reported before extubation.

Finally, we agree with the authors that improved outcomes could certainly have been obtained by applying NIV in a more experienced center, in selected patients, and earlier in postextubation ARF.

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In Reply: We share the concern of Drs Girault and Auriant about the discrepancy in results among studies of NIV, not only in the setting of postextubation respiratory distress but in most settings. Discordant study results generally arise as a result of differences in either the population studied, the application of the technology or treatment, or the way outcomes are defined. We believe the first 2 may be most important in this instance. Our patient population was heterogeneous, representing the diverse population found in ICUs. The one randomized trial to which Girault and Auriant alluded primarily include patients after having undergone lung resection.[1]This group represents patients with obstructive lung disease, a population that the literature has previously suggested strongly benefit from NIV. We specifically excluded such patients after the first year, resulting in fewer than 25% of patients with any history of obstructive lung disease and only 10% for which this was a factor in ICU admission.

How NIV is applied in the setting of postextubation respiratory distress may vary among centers and be related to varying success rates. Aside from differences in ventilators and interfaces, placement of the interface, choice of initial pressures, subsequent pressures, titration and specific interactions with patients may influence acceptance and success of the technology. Centers that are most experienced may develop superior approaches that are not easily summarized. Although our center may lack the expertise of others, we believe we are at least average. If different methods of applying NIV can lead to such discrepancy in outcomes, then there should be a greater emphasis on initial and ongoing training of personnel.

We agree that discrepant results are of concern, but we believe that exploring these discrepancies offers an opportunity to learn more about the technology. Different results are less likely due to bad vs good studies than to differences in populations studied (which we believe contributed to at least some of the differences found) or how the application is applied. We believe that the latter is very important to explore. Perhaps a systematic review of how NIV is applied across all studies may demonstrate that the methods used by some investigators are truly superior to those used by others. If so, then universal adoption of the superior method would benefit all.

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1. Auriant I, Jallot A, Hervé P, et al. Noninvasive ventilation reduces mortality in acute respiratory failure following lung resection. *Am J Respir Crit Care Med*. 2001; 164:1231-1235.

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Spirituality and Chronic Illness

To the Editor: In his Clinical Crossroads article, Dr Koenig[1] discussed an elderly woman with chronic illness and strong religious beliefs. Although the article's purpose was to illuminate research that shows religious beliefs can have a therapeutic effect on chronic illness, we are concerned that some pain treatment options were not explored.

The patient's medical history reveals that her care team unsuccessfully tried many different treatment regimens; however, the article does not mention whether she was ever referred to a pain specialist. There are many other anticonvulsants, antidepressants, and opioids that have demonstrated a therapeutic benefit for some types of neuropathic pain.[2-4] Implantable therapies, including spinal cord stimulation and intrathecal infusions, might also be helpful in carefully selected patients.[5] In addition, specific psychological interventions can be effective in treating severe chronic pain.[6]

We would ask clinicians to consider referring patients with severe pain to a pain specialist. In the elderly population in whom painful complaints are sometimes overlooked, pain management referrals may be important to ensure that all options have been properly evaluated.[7]

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1. Koenig HG. An 83-year-old woman with chronic illness and strong religious beliefs. *JAMA*. 2002;288:487-493.
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To the Editor: In his discussion of the impact of spiritual beliefs and the benefit to patients, Dr Koenig hypothesizes that the improved health outcomes may be due to deep relaxation, distraction from pain, alteration of neural pathways, and hormonal changes.[1] He also points out that 90% of Americans turn to religion in times of stress. These millions of people are not praying for the mechanisms suggested by Koenig, but for divine intervention. Yet not one word in his article addresses even the notion of a divine power.

Physicians treat not only physical symptoms but also the soulful aspects of existence, including memory, emotions, and feelings. There is an unseen but essential life force that grants life. That is the reason that at the point of death we say the person has expired. We find Koenig's discussion of the role of the physician in discovering and using the spiritual beliefs of patients to be sensitive and wise. As he states, some patients "may refuse to speak with clergy because they are angry with God . . . not all patients, however, wish to talk to unfamiliar chaplains . . . (but) may be willing to discuss these issues with a caring physician who is known and trusted." Although most patients believe that their physicians should address spiritual issues, there are those who think such discussions would be inappropriate.[2] As Koenig has stated, "Bringing spirituality back into medicine may be what we all need."[3] Diagnosis and treatment is a catalyst for wellness. Physicians cannot provide but only promote healing. We believe that the spirit of God provides the healing and that we are His physicians.

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1. Koenig HG. An 83-year-old woman with chronic illness and strong religious beliefs. *JAMA*. 2002;288:487-493.
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To the Editor: Dr Koenig's Clinical Crossroads article[1] supports the need for a holistic perspective of health, one incorporating spiritual factors with physical, psychological, and social determinants.[2] The discussion also highlighted many challenges that physicians face when patients introduce religious or spiritual concerns. Social, psychological, and now spiritual information is encouraged in clinical assessments. Such information is increasingly considered in therapeutic planning, and can be useful in many ways. For example, the frequency of religious service attendance may be a proxy for functional status in disabled elderly patients,[3] representing important information for physicians who care for this population. However, a primary consideration for clinicians is the way they frame and integrate religious and spiritual issues and concerns for their patients.

The article focused on religious and spiritual coping strategies, pathophysiological mechanisms, and outcomes data in determining the appropriateness of the patient's belief system in the clinical encounter. This unusual application of health services research to resolve an ethical dilemma may explain why Koenig's review of research linking religious and spiritual variables and health-related outcomes cannot provide clear recommendations for the patient. It is unclear how the admonition to "keep it up" or the call for physician support of the patient belief system go beyond the fundamental elements of a caring, competent patient-physician relationship. These reactions do not seem to respond to the uniquely spiritual and religious concerns raised by a patient.

Religion and spirituality are primarily social and cultural constructs, and the incorporation of these perspectives can provide direction and clarity for physicians. For example, explanatory models have been used to describe the ways in which illness is interpreted, and patients often include reli-

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gious and spiritual perspectives into their explanatory models particularly when suffering is involved.[4] Although in this case the patient narrative is limited and we know disappointingly little about her understanding of her illness, her voice is characterized by positive thinking, and her explanatory model is remarkable in its self-efficacy and agency beliefs.[5] Physicians who respond to patients' religious and spiritual concerns must include a social or cultural viewpoint in their undertaking, and the failure to do so reduces the illness experience to a series of biomedical, social, and now spiritual determinants.

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1. Koenig HG. An 83-year old woman with chronic illness and strong religious beliefs. *JAMA.* 2002;288:487-493.
2. Institute for the Future. *Health and Health Care 2010: The Forecast, The Challenge.* San Francisco, Calif: Jossey-Bass; 2000.
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In Reply: I agree with Drs Burton and Arens that there are many biological, psychological, and surgical options available for treating older patients with chronic pain, and all should be exhausted before concluding that religion or prayer is the only solution. However, it is the spiritual approach that is most often overlooked,[1] and hence the focus of my article.

Drs Flynn and Fulton state that I did not acknowledge the possibility that a supreme being or divine power may be involved in relief of pain, and that I did not acknowledge other health benefits associated with religion. As a scientist, I seek to understand the effects of religion on health in terms of natural mechanisms—psychosocial, behavioral, and physiological pathways known to influence health and well-being. I agree that the divine has much to do with the health and healing of patients and that we as physicians are indeed instruments of that power, but I base this belief on my faith not on science.[2] There are some answers that science cannot provide and some answers that faith cannot provide; both may be essential for good medicine.

Dr Daaleman raises an important concern about how physicians should respond to the uniquely spiritual or religious issues raised by patients. He emphasizes the necessity of including a social or cultural viewpoint when doing so. I agree that my recommendation to the patient's physician to encourage her to "keep it up" was hardly a comprehensive way of addressing her uniquely religious or spiritual concerns. But how much can the average physician with little education or training in this area do aside from learning about, respecting, and supporting the beliefs of the patient? Although referral does not get physicians entirely off the hook, there are professionals within the health care system who are uniquely trained to address spiritual concerns in their overall context—chaplains and pastoral counselors—and physicians should fully utilize their expertise.[3]

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1. Koenig HG. *Chronic Pain: Biomedical and Spiritual Approaches*. New York, NY: Haworth Press; 2002.
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Prematurity and Later Cognitive Outcomes

To the Editor: In their meta-analysis, Dr Bhutta and colleagues[1] found cognitive and behavioral deficits among school-age children who were born preterm. However, we have concerns about the scoring system used to assess quality of the studies included in the meta-analysis. The 10-point score had 6 items (Table 1) that appear to take on values of either 0, 1, or 2, yielding a possible range of 0 to 12 for the scale. However, the label "NA," which appears in 3 of 18 cells and is defined as "data not available," presumably means "not applicable." Therefore, 2 of the 6 items ("Demographic" and "Socioeconomic") would score a maximum of 1, and "Study design" would never require a score of 0. The relative weightings for the items are not explained or justified. It was also unclear how half-points were scored, but presumably such scoring reflects the averaging of 2 scores. When we applied this scoring system to one of our own studies[2] we calculated a score of 9 of 10, instead of the 7 of 10 assigned by Bhutta et al.

Having rated the studies, Bhutta et al then reported no statistically significant differences in either the Wechsler Intelligence scores or in the relative risks for attention deficit hyperactivity disorder between the "high-quality" and "low-quality" studies. This suggests either that the scoring system was insensitive and did not discriminate between the quality of the studies, or that it was not worth the effort to discriminate for quality as it did not affect interpretation of the results.

Furthermore, the selection of quality variables was incomplete. For outcome assessments of preterm children in general, important quality markers might include assessment by experts blinded to birth weight or gestational age, use of known diagnostic criteria for the outcomes of interest with little or no observer variation, and higher follow-up rates than the 70% permitted by Bhutta et al. Children who are more difficult to follow up have poorer neurosensory outcomes than those who are more likely to return for follow-up.[3,4] We reported a 12.7-point difference in IQ (95% confidence interval, 7.4-18.0) at 5 years of age between the 75% of preterm children followed up with ease and the 25% of children followed up with difficulty.[4] If we had not pursued those latter 25% children, the overall follow-up rate would have been

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71%, the reported mean IQ much higher, and the prevalence of neurosensory disability much lower.

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In Reply: In response to Dr Doyle and colleagues, specific criteria for assessing the quality of observational studies have not been developed or validated. Furthermore, the validity of quality scores even for randomized trials may be questionable.[1] In our meta-analysis, we present the first attempts to identify some of the criteria that can be used for assessing the quality of observational studies. We make no claims to the completeness or validation of this method.

We agree that the "NA" label should read "not applicable" rather than "data not available," thus making a 10-point scale that measures 2 broad parameters, namely study procedures and adequacy of data reporting. To evaluate study procedures, we looked at sampling techniques, study design (prospective cohorts vs retrospective cohorts), and matching of cases and controls. To evaluate the data reporting, we examined the details available for demographic data, socioeconomic data, and neurologic outcomes.

Space considerations prevented us from describing the scoring rationale for each parameter. The many different ways of reporting demographic and socioeconomic data compelled us to grade them as either complete or incomplete only. We only included studies with a case-control design; therefore a score of 0 was not assigned, and prospective studies were weighted higher than retrospective studies. Thus, studies with no control groups would receive a 0 for study design, and were not included in our meta-analysis. Doyle et al are correct to assume that half-points reflect an average of 2 scores. We believe that our independent evaluations of their previous research are less likely to be biased than the authors' own scoring of it.

There were no significant differences in cognitive outcomes between high- and low-quality studies, perhaps because the scale was not sensitive enough or because there were minimal differences in the quality of the selected studies. Poor-quality studies had already been excluded by the stringent application of our inclusion and exclusion criteria. We agree that the blinding of observers to gestational age or birth weight would be a desirable marker of study quality and should have been included. Researchers in this field must develop consensus about using fewer well-validated tools for assessment of cognition and behavior rather than the current plethora of methods. An attrition rate of less than 30% was selected arbitrarily and excluded a large number of studies. A lower attrition rate (25% or 20%) may have excluded many more studies that were otherwise well designed and executed. But we concur with Doyle et al that a criterion for lower attrition rates will provide more accurate results.

Our quality score was developed strictly for this meta-analysis and may provide a framework for assessing study quality in other meta-analyses of observational studies. Attempts to refine this method are laudable, but may be limited by the incomplete details available from most observational studies in this field.

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RESEARCH LETTER

Aspiration of a Dental Appliance in a Patient With Alzheimer Disease

To the Editor: Dental caries is associated with halitosis, poor cosmesis, and discomfort. Bacterial overgrowth in the oral cavity can lead to aspiration pneumonia or endocarditis in elderly patients.[1,2] In the nursing home population, poor oral hygiene is common, with a 50% prevalence of dental caries.[3] This report describes an unexpected consequence of dental caries in a demented patient.

Report of a Case. A 76-year-old male resident of a local nursing home was brought to the emergency department with a 3-day history of fever and cough. He had severe Alzheimer dementia and was unable to communicate. He had been fed through a gastrostomy tube for the past several years. Physical examination was remarkable for copious oral secretions, severe halitosis, and poor dentition. A chest radiograph revealed an aspirated dental bridge lodged in the cervical esophagus (FIGURE). The patient was taken to the operating room for direct laryngoscopy, bronchoscopy, and esophagoscopy with removal of the foreign body. A large amount of purulent material was suc-

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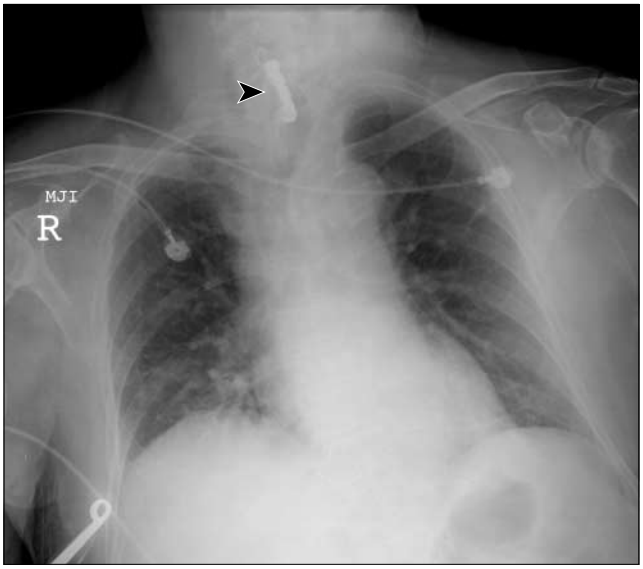
Figure. Radiograph Showing Aspirated Dental Bridge Lodged in the Cervical Esophagus



tioned through a perforation in the esophagus at the site of the foreign body. Significant edema of the larynx and hypopharynx was noted.

The dental appliance was a bridge of 4 teeth that had evidently been held in position by the roots of the 2 remaining teeth. Severe caries had eroded the roots, permitting aspiration of the entire unit. Postoperative computed tomography of the neck and chest revealed a retroesophageal abscess tracking into the mediastinum, with surrounding mediastinitis. After discussion of the risks and benefits of proceeding with open surgical drainage, the family elected comfort care only. The patient died shortly thereafter.

Comment. In this patient, an aspirated dental bridge secondary to dental caries led to mediastinitis and death. In all likelihood, this bridge had been aspirated several weeks prior to presentation, but because the patient was fed through a gastrostomy tube, no symptoms were identified prior to esophageal perforation. Because many nursing home patients are unable to communicate to staff, it is critical that such patients receive prophylactic dental hygiene.[3-5]

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CORRECTION

Incorrect Table: In the Original Contribution entitled "Menopausal Hormone Replacement Therapy and Risk of Ovarian Cancer" published in the July 17, 2002, issue of THE JOURNAL (2002;288:334-341), there were errors in Table 1. On page 336, in Table 1, the last 4 lines of the table are replaced by the 4 lines below in the **TABLE**.

Table. Prevalence of HRT Use by Selected Factors*

	% of Person-Years†						
Factor	None	ERT Only	EPRT Following ERT	EPRT Only	ERT Only, Unknown Use of Progestins	Unknown HRT	Total Person-Years‡
BCDDP participant type							
Breast surgery; no malignant disease	45	32	6	7	5	5	246 385
No surgery performed or recommended	46	30	6	7	6	5	248 813
Recommended for surgery	49	28	6	7	6	5	94 015

*HRT indicates hormone replacement therapy; ERT, estrogen replacement therapy; EPRT, estrogen-progestin replacement therapy; and BCDDP, Breast Cancer Detection Demonstration Project.
†Percentages may not sum to 100 because of rounding.
‡Excludes 3884 person-years among women with progestins-only use and 402 person-years among women with "progestin, estrogen unknown" use.

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